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Effect of serum uric acid level on maternal and neonatal outcome in patients with hypertensive disorders of pregnancy at HSK Hospital, Bagalkot: A prospective and observational study

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ABSTRACT

Background: Uric acid, a metabolite of purine metabolism, is considered as a marker of hypertensive disorder of pregnancy (HDP) severity. An increase in serum uric acid level in pregnant mothers has been found to be associated with the disease severity. **Aims and Objectives:** The present study intended to evaluate the effect of serum uric acid level in maternal and neonatal outcome in cases of hypertensive disorders of pregnancy. **Materials and Methods:** This prospective and observational study was conducted on patients with HDP from December 2017 to April 2019. The study was conducted on 274 subjects who visited the Department of Obstetrics and Gynecology, HSK Hospital, Bagalkot. The participants were categorized into two groups according to their serum uric acid level (<6 mg/dL and ≥6 mg/dL). Serum uric acid was estimated by enzymatic colorimetric method. Maternal and neonatal outcomes were recorded. Follow-up was done till the discharge of the mother and child from the hospital. Data were analyzed using coGuide software. **Results:** The majority of the participants were in the age group of 18–23 year (52.91%). No significant association was observed between serum uric acid groups and maternal parameters such as parity, gestational age, onset of labor, mode of delivery, and maternal complications. (P>0.05). There was statistically no significant difference between serum uric acid groups in neonatal outcomes such as Apgar score 1 min and 5 min, IGUR, NICU admission, and reason for NICU admission (P>0.05) except for still birth. Still birth was found to be more in patients with serum uric acid ≥6mg/dl (19.64%) group compared to <6 mg/dl (8.64%) with P=0.008. **Conclusion:** This study shows that there was no significant association between adverse maternal and neonatal outcomes with increased level of serum uric acid.

Key words: Gestational hypertension; Uric acid; Pregnancy outcome; Hemolytic anemia elevated liver enzymes levels, Low platelet count syndrome

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INTRODUCTION

One of the most common medical disorders during pregnancy is hypertensive disorders, known as hypertensive disorder of pregnancy (HDP), which accounts for the majority of the perinatal and maternal morbidity and mortality.[1] Reports have shown that around 3–8% of all HDP are pre-eclampsia, and around 10–15% of maternal death has been reported across the globe, due to pre-eclampsia and eclampsia together.[2,3] Maternal complications such as severe hypertension, eclampsia, and HELLP syndrome (hemolytic anemia, elevated liver

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enzymes levels, and low platelet count) or even neonatal morbidity and maternal death have been observed.[4] Fetal complications such as growth restriction and small for gestational age, preterm births, neonatal deaths, and serious long-term neonatal morbidity have been reported in association with preeclampsia.[5]

Uric acid, a metabolite of purine metabolism, is considered as a marker of HDP severity. An increase in serum uric acid level in pregnant mothers has been found to be associated with the disease severity.[6] It was also found that before the onset of proteinuria or hypertension in HDP, there was an increase in uric acid.[7] Impaired renal clearance of uric acid, elevated breakdown of tissues, acidosis, and an increase in dehydrogenase or xanthine oxidase enzyme were believed to be the reasons for higher levels of uric acid levels in the serum of pregnant women with HDP.[8,9] A reduction in the rate of glomerular filtration is the main reason for impaired clearance of uric acid from kidney, reduction in secretion and elevated absorption results in higher serum uric acid levels in individuals with HDP. A decrease in the serum uric acid level to about to 3 mg/dL or more has been observed during the first trimester in pregnant women, due to higher blood flow in kidney and uricosuric effects of estrogen.[9] Followed by this, an elevation in the serum uric acid level occurs in the third trimester, reaching up to 4–5 mg/dL at term. However, a slightly higher serum uric acid level was observed in HDP prone pregnant women, especially in the first trimester of their pregnancy.[10]

Assessing the predictive ability of uric acid level in pregnancy aids in timely interventions and provision of better care facility in HDP prone pregnant women.[11] Hence, the present study intended to evaluate the effect of serum uric acid level on maternal and neonatal outcome in cases of hypertensive disorders of pregnancy at HSK Hospital, Bagalkot.

Aims and objectives

Aims:

To evaluate the relationship of serum uric acid level to maternal and perinatal outcome in patients with hypertensive disorders of pregnancy.

Objectives:

1) To estimate the levels of serum uric acid in patients with hypertensive disorders of pregnancy.
2) To evaluate the maternal and perinatal outcome.

MATERIALS AND METHODS

Study population and study site

Patients with HDP admitted to the Department Of Obstetricsand Gynecology, HSK Hospital, Bagalkot.

Study duration

The study duration was 1 year and 4 months from December 2017 to April 2019.

Inclusion criteria

The following criteria were included in the study:

Patients delivering in HSK hospital from December 2017 to April 2019

Patients diagnosed with HDP.

Exclusion criteria

Patients with known renal disorder, diabetes mellitus, cardiovascular disease, pregnancies with congenital anomalies in fetus, and history of treatment for chronic hypertension were excluded from the study.

Study design

This study was a prospective and observational study.

Sample size and sampling method

All the eligible 274 subjects who visited during the study period were included in the study. The sampling was universal.

Ethical considerations

Ethical clearance was obtained from the Institute's Ethics Committee (Human Studies). Ethical clearance No: SNMC/IECHSR/2017-18/A-46/1.1 Data confidentiality was maintained. Written informed consent was obtained from the patients.

Data collection tool

Gestational hypertension was diagnosed with new onset systolic blood pressure of 140 mm Hg or more or a diastolic blood pressure of 90 mm Hg or more, or both, on two occasions at least 4 h apart after 20 weeks of gestation, in a woman with a previously normal blood pressure in the absence of proteinuria and without biochemical or hematological abnormalities.

Pre-eclampsia

Hypertension developing after 20 weeks' gestation and the coexistence of one or more of the following new onset conditions:[12]

1 Proteinuria 300 mg or more per 24h urine collection or Protein/creatinine ratio of ≥30mg/mmol (0.3mg/mg) or Dipstick reading of 2+.
2) Other maternal organ dysfunction such as renal insufficiency (creatinine >90 umol/L), liver involvement (elevated transaminases and/or severe right upper quadrant or epigastric pain), neurological complications (examples include eclampsia, altered mental status, blindness, stroke, or more commonly hyperreflexia when accompanied

by clonus, severe headaches when accompanied by hyperreflexia, and persistent visual scotomata) hematological complications (thrombocytopenia, DIC, and hemolysis)
3) Uteroplacental dysfunction such as fetal growth restriction

Serum uric acid was estimated by enzymatic colorimetric method in all hypertensive pregnancy patients. For estimation of serum uric acid, blood sample was collected from venipuncture. In case of multiple estimations before delivery, the value closest to delivery was used in the analysis. The participants were categorized into two groups according to their serum uric acid level (<6 mg/dl and ≥6 mg/dl)

Age, parity, gestational age, maternal complications like onset of labor, mode of delivery, maternal complication, neonatal outcomes like APGAR score at1 min and at 5 min, still birth, and intrauterine growth restriction reason for NICU admission were recorded. Follow-up was done till the discharge of the mother and child from the hospital. Consent was obtained from the patient and data confidentiality was maintained.

Statistical analysis

The Chi-square test and Fisher's exact test were used to evaluate baseline parameter, maternal outcome, and neonatal outcomes between serum uric acid. P<0.05 was considered to indicate statistical significance. Data were analyzed using coGuide software, V.1.03.[13]

RESULTS

Out of total 3500 deliveries, during the study period from December 2017 to April 2019 of which 388 (9%) were found HDP. A total of 274 subjects were included in the final analysis. Out of 274, patients with HDP with a different degree of hypertension (mild PE, sever PE, impending eclampsia/eclampsia, and gestational hypertension) there were 162(59.12%) with serum uric acid <6 mg/dl and 112(40.88%) with serum uric acid ≥6 mg/dL.

The majority of patients in both groups were within the age group of 18–23 years [84 (51.85%) in<6mg/dl and 61 (54.46%) in ≥6 mg/dL]. It can be seen that the patients with serum uric acid <6mg/dL were younger than the patients with serum uric acid ≥6 mg/dL. There is no significant association between serum uric acid level and parity. The majority of patients in both the groups were nulliparous. This study shows that 9.82% of patients with serum uric acid ≥6 mg/dL delivered before 32 completed weeks compared to 4.32% of patients with serum uric acid <6 mg/dL. About 34.57% of patients with serum uric acid <6 mg/dl were delivered after 37 completed weeks compared to 19.64% of patients with serum uric acid ≥6 mg/dl. Among the patients with serum uric acid <6 mg/dL, 55.55% had milder form of HDP (Gestational hypertension and Mild PE) compared to 44.45% had severe form of HDP (Sever PE, Impending eclampsia, and Eclampsia). Among the patients with serum uric acid ≥6 mg/dl, 45.54% milder form of HDP (Gestational hypertension and Mild PE) compared to 54.46% had severe form of HDP (Sever PE, Impending eclampsia, and Eclampsia) (Table 1).

There was no significant association between the two groups of serum uric acid level and onset of labor. The study shows that 5.36% of patients with serum uric acid ≥6 mg/dL was delivered by vacuum or forceps delivery compare to 1.85% of patients with serum uric acid <6 mg/dl. Maternal complications such as abruptio placenta, postpartum hemorrhage, blood transfusion and HELLP syndrome were almost near double in patients with serum uric acid ≥6 mg/dL compare to patients with serum uric acid <6 mg/dl. No significant association noted between the two groups of serum uric acid level and eclampsia (Table 2).

Table 1: Comparison of baseline parameter between serum uric acid (n=274)

Parameter	Serum uric acid		P value
	<6mg/dl (n=162)	≥6 mg/dl (n=112)	
Age group (in years)			
18–23	84 (51.85%)	61 (54.46%)	0.024
24–29	63 (38.89%)	30 (26.79%)	
30 and above	15 (9.26%)	21 (18.75%)	
Parity			
0	86 (53.09%)	67 (59.82%)	*
1	47 (29.01%)	30 (26.79%)	
2	21 (12.96%)	9 (8.04%)	
3	4 (2.47%)	4 (3.57%)	
4	3 (1.85%)	2 (1.79%)	
5	1 (0.62%)	0 (0%)	
Gestational age (in weeks)			
<28 weeks	0 (0%)	2 (1.79%)	*
28–<32	7 (4.32%)	11 (9.82%)	
32–<34	13 (8.02%)	6 (5.36%)	
34–<37	13 (8.02%)	19 (16.96%)	
37–<39	56 (34.57%)	22 (19.64%)	
39–<41	63 (38.89%)	48 (42.86%)	
≥41 weeks	10 (6.17%)	4 (3.57%)	
Type of HDP			
Milder form of HDP			
Gestational hypertension	55 (33.95%)	28 (25%)	0.333
Mild pre-eclampsia	35 (21.6%)	23 (20.54%)	
Severe form of HDP			
Severe pre-eclampsia	42 (25.93%)	33 (29.46%)	
Impending eclampsia	30 (18.52%)	28 (25%)	

*No statistical test was applied – due to o subjects in the cells

Among the patients with serum uric acid, the majority of babies in both groups were within the birth weight of 2500–<4000 g. There was statistically no significant difference between serum uric acid in neonatal outcomes such as Apgar score at1 min (P=1.000) and at 5 min (P=0.713), IGUR (P=0.605), NICU admission (P=0.222), and reason for NICU admission (among the live borns) (P=0.399). The study shows significant association between the two groups of serum uric acid level and still birth. (P<0.008). Still birth was more (19.64%) in patients with serum uric acid ≥6 mg/dL compares to patients with serum uric acid <6 mg/dL (8.64%)(Table 3).

Table 4 shows that the mean±SD of serum uric acid was 5.59±1.48 in ANOVA test.

DISCUSSION

This study included 274 participants with HDP. The majority of participants (52.92%) were in the age group 18–23 years which is the common age of pregnancy in developing countries such as India due to early marriage and early pregnancy which is in keeping with the religion, tradition, and culture. In the present study, spontaneous vaginal delivery and cesarean section were almost similar in the two groups. However, Zangana et al.,[14] report that women were more often delivered by cesarean section when serum uric acid ≥6 mg/dL when compared with <6 mg/dl. Furthermore, the study conducted by Tejal and Astha,[15] showed that cesarean section incidence increased by 3.4-fold in patients with a uric acid level ≥6mg/dL as compared to those with a level of <6mg/dL.

In our study, incidence of maternal complications such as abruptio placenta, postpartum hemorrhage, blood transfusion, and HELLP syndrome were higher in patients with serum uric acid ≥6 mg/dL compared to patients with serum uric acid <6 mg/dL.

In a study conducted by Saldanhaet al.,[16] maternal complications such as proteinuria, coagulopathy, need for blood/platelet transfusion, eclampsia, and HELLP syndrome were higher in patients with serum uric acid ≥5 mg/dL as compared to those with <5 mg/dL. Their study concluded that significant correlation exists between elevated SUA (≥5mg/dL), abruptio placentae, HELLP syndrome, deranged coagulation profile, etc. Similar

Table 2: Comparison of maternal outcomes between serum uric acid (n=274)

Parameter	Serum uric acid		P value
	<6 mg/dl (n=162)	≥6 mg/dl (n=112)	
Onset of labor			
Spontaneous	74 (45.68%)	45 (40.18%)	0.367
Induced	88 (54.32%)	67 (59.82%)	
Mode of delivery			
Spontaneous vaginal delivery	73 (45.06%)	49 (43.75%)	*
Breech vaginal delivery	1 (0.62%)	2 (1.79%)	
Vacuum or forceps delivery	3 (1.85%)	6 (5.36%)	
Cesarean section	85 (52.47%)	54 (48.21%)	
Laparotomy	0 (0%)	1 (0.89%)	
Maternal complication (n=199)			
Oligohydramnios	28 (26.92%)	23 (24.21%)	0.441
Abruptio placenta	3 (2.88%)	6 (6.32%)	
PPH	4 (3.85%)	7 (7.37%)	
Blood transfusion	9 (8.65%)	14 (14.74%)	
Platelet transfusion	14 (13.46%)	10 (10.53%)	
HELPP syndrome	1 (0.96%)	2 (2.11%)	
MSL	45 (43.27%)	33 (34.74%)	
Eclampsia	20 (12.35%)	22 (19.64%)	0.099

*No statistical test was applied – due to o subjects in the cells,
MSL: Meconium-stained liquor, PPH: Postpartum hemorrhage

Table 3: Comparison of neonatal outcomes between serum uric acid (n=274)

Parameter	Serum uric acid		P value
	<6 mg/dl (n=162)	≥6 mg/dl (n=112)	
Birth weight			
<1000	7 (4.32%)	5 (4.46%)	*
1000–<1500	12 (7.41%)	17 (15.18%)	
1500–<2500	48 (29.63%)	40 (35.71%)	
2500–<4000	94 (58.02%)	50 (44.64%)	
≥4000	1 (0.62%)	0 (0%)	
APGAR 1 min (n=238)			
<5	8 (5.41%)	4 (4.44%)	
≥5	140 (94.59%)	86 (95.56%)	1.000†
APGAR 5 min (n=238)			
<7	5 (3.38%)	2 (2.22%)	0.713†
≥7	143 (96.62%)	88 (97.78%)	
IUGR	33 (20.37%)	20 (17.86%)	0.605
Still birth	14 (8.64%)	22 (19.64%)	0.008
NICU admission (n=238)	25 (16.89%)	10 (11.11%)	0.222
Reason for NICU admission (among the live borns) (N=25)			
Birth asphyxia	5 (20%)	1 (10%)	
LBWM	17 (68%)	6 (60%)	0.399
RDS	3 (12%)	3 (30%)	

*No statistical test was applied – due to o subjects in the cells, †-Fisher's exact test,
IUGR: Intrauterine growth restriction, LBWM: Low birth weight management,
RDS: Respiratory distress syndrome

Table 4: Distribution of sample according to mean serum uric acid level among the patient with different level of hypertension

Type of hypertension	Serum uric acid (mg/dL)	95% Confidence interval	
	Mean±SD	Lower	Upper
Mild Pre-eclampsia	5.68±1.35	5.33	6.04
Severe pre-eclampsia	5.65±1.48	5.31	5.99
Impending eclampsia/ Eclampsia	5.68±1.69	5.24	6.13
Gestational Hypertension	5.40±1.41	5.10	5.72
Total	5.59±1.48	5.42	5.77

observation was also reported by Pereira et al.,[17] and Nischintha et al.[18]

Increased birth weight was detected for babies born to mothers with serum uric acid<6mg/dL compared to ≥6mg/dL group, but was not statistically significant. Still birth was observed to be more in subjects with hyperuricemia. (8.64%vs. 19.64%) The difference in the rates of stillbirth was statistically significant. Similar observations were noted for low birth-weight (Pareira et al.,[17] Nischintha et al.,[18]). This shows a clear association of hyperuricemia with adverse fetal outcomes. Similar findings have also been reported by Kondareddy and Prathap[6]

In a study conducted by Saldanha et al.,[16] who used a cut off of 5mg/dL Serum uric acid, fetal complications were higher in women with serum uric acid >5mg/dL. The present study revealed no significant association between the two groups in NICU admission. There was also no significant association in Apgar score at 1 min and at 5 min. Similar negative association was noted for Apgar score in study conducted by Zangana et al.[14] In contrast, the study by Priya et al.,[19] Shows significant association between increased levels of serum uric acid levels and APGAR Score at 5min. In the present study, the mean±SD of serum uric acid in patients with different severity of HDP was 5.59±1.48. A value of 6.365±1.77 was obtained in a study conducted by Zangana et al.[14] It is clear that there was no significant association between adverse maternal and neonatal outcomes with increased level of serum uric acid in the present study.

Limitations of the study

The present study was conducted in a single center and with a smaller sample size. In the future, we can plan of conducting a study for longer duration and with more sample size.

CONCLUSION

This study shows that there is an association between adverse fetal outcomes and level of serum uric acid. However, these adverse outcomes are not limited to the group with high serum uric acid levels and, hence, a cutoff value predicting adverse neonatal outcomes cannot be suggested from these results. This supports that the estimation of serum uric acid is done as a routine in clinical practice in women with pre-eclampsia, it does not guide the management. Although the serum uric acid levels are high, clinicians do not take the decision to employ the definitive management strategy in pre-eclampsia, which is delivery, based solely on this parameter.

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Authors Contribution:
SH- has conceptualized the study and played primary role in compiling, analysis, and interpretation of the data. All the drafts were prepared, reviewed, and final draft was approved by **NP, VCR, SR, SH, SR**. **NP, VCR, SR, SH**- SRhave contributed in fine tuning of the proposal, contributed in data collection and entry,reviewed the results, and contributed to preparation and review of drafts. All the authors have read and approved final version of the manuscript. All the authors take complete responsibility for the content of the manuscript.

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